

REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Applicants note with appreciation the indication that claim 18 would be allowable if rewritten in independent form. Claim 18 has been amended accordingly. In addition, claims have been amended to depend from claim 18. Claim 25 has also been amended to include the step of administering radiotherapy to the patient. Moreover, claim 27 has been indicated to be allowable. As noted by the Examiner, the art fails to teach a radiotherapy step of treatment following the stereotactic injection of anticancer loaded microspheres.

Applicants note the "Election Requirement" indicated on page 2 of the Official Action. The prior Official Actions required an "election of species" for examination purposes. Applicants note the statement that "upon the allowance of a generic claim applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all limitations of an allowed generic claim as provided by 37 CFR 1.141." Page 2. The indication that claims 21 and 23 are withdrawn from examination is thus in error. Upon allowance of a generic claim, these claims should be considered since they depend from the generic independent claim, claim 18. Once claim 18 is indicated as being allowable, claims 21 and 23 should also be considered and allowed.

Claim 14 was rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is now moot in view of the amendment of the claim. The trademark term was deleted in favor of identifying the surfactant as "polysorbate." This is an art recognized term at the time the application was originally filed, as shown by the pages from the *Handbook of Pharmaceutical Excipients*, enclosed herewith.

Claims 1-7, 9-13, 14, 15, 17, 19, 20, 22 and 24-26 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Emerich et al. This rejection is believed to be rendered moot by the instant amendment.

The Official Action indicated at pages 5-6 that claim 18 would be allowable if rewritten in independent form including all recitations of the claim from which it depends. This has been done in the instant amendment. The rejected claims have been amended to depend from claim 18. Accordingly, all of the claims are believed to now be in condition for allowance.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

Claims 1-9, 16, 17 and 20 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Boisdstron-Celle et al. This rejection is believed to be rendered moot by the instant amendment.

As stated *supra*, claim 18 was indicated to be allowable if rewritten in independent form including all recitations of the claim from which it depends. This has been done in the instant amendment. The rejected claims have been amended to depend from claim 18. Accordingly, all of the claims are believed to now be in condition for allowance.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (650) 622-2360 so that prosecution of the application may be expedited.

Respectfully submitted,

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Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by
Ainley Wade and Paul J Weller

**American Pharmaceutical Association
Washington**

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**The Pharmaceutical Press
London**

Polyoxyethylene Sorbitan Fatty Acid Esters

1. Nonproprietary Names

BP: Polysorbates 20, 60 and 80
 PhEur: Polysorbatum 20, 60 and 80
 USPNF: Polysorbates 20, 40, 60 and 80

2. Synonyms

Synonyms of selected polysorbates are shown below, *see also* Section 3.

Polysorbate	Synonym
Polysorbate 20	<i>Armotan PML 20</i> ; <i>Capmul POE-L</i> ; <i>Crillet 1</i> ; E432; <i>Glycosperse L-20</i> ; <i>Hodag PSML-20</i> ; <i>Liposorb L-20</i> ; <i>Liposorb L-20K</i> ; <i>Montanox 20</i> ; sorbitan monododecanoate poly(oxy-1,2-ethanediyl) derivatives; polyoxyethylene 20 laurate; <i>Protasorb L-20</i> ; <i>Tween 20</i> .
Polysorbate 21	<i>Crillet 11</i> ; <i>Hodag PSML-4</i> ; <i>Protasorb L-5</i> ; <i>Tween 21</i> .
Polysorbate 40	<i>Crillet 2</i> ; E434; <i>Glycosperse S-20</i> ; <i>Hodag PSMP-20</i> ; <i>Liposorb P-20</i> ; <i>Montanox 40</i> ; <i>Protasorb P-20</i> ; sorbitan monohexadecanoate poly(oxy-1,2-ethanediyl) derivatives; <i>Tween 40</i> .
Polysorbate 60	<i>Armotan PMS 20</i> ; <i>Capmul POE-S</i> ; <i>Crillet 3</i> ; E435; <i>Glycosperse S-20</i> ; <i>Hodag PSMS-20</i> ; <i>Liposorb S-20</i> ; <i>Liposorb S-20K</i> ; <i>Montanox 60</i> ; <i>Polycon T 60 K</i> ; polyoxyethylene 20 stearate; sorbitan monooctadecanoate poly(oxy-1,2-ethanediyl) derivatives; <i>Protasorb S-20</i> ; <i>Tween 60</i> .
Polysorbate 61	<i>Crillet 31</i> ; <i>Hodag PSMS-4</i> ; <i>Protasorb S-4</i> ; <i>Tween 61</i> .
Polysorbate 65	<i>Crillet 35</i> ; E436; <i>Glycosperse TS-20</i> ; <i>Hodag PSTS-20</i> ; <i>Liposorb TS-20</i> ; <i>Liposorb TS-20K</i> ; <i>Montanox 65</i> ; sorbitan trioctadecanoate poly(oxy-1,2-ethanediyl) derivatives; <i>Protasorb STS-20</i> ; <i>Tween 65</i> .
Polysorbate 80	<i>Armotan PMO 20</i> ; <i>Capmul POE-O</i> ; <i>Crillet 4</i> ; <i>Crillet 50</i> ; E433; <i>Glycosperse O-20</i> ; <i>Hodag PSMO-20</i> ; <i>Liposorb O-20</i> ; <i>Liposorb O-20K</i> ; <i>Montanox 80</i> ; polyoxyethylene 20 oleate; (Z)-sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; <i>Protasorb O-20</i> ; <i>Tween 80</i> .
Polysorbate 81	<i>Crillet 41</i> ; <i>Hodag PSMO-5</i> ; sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; <i>Protasorb O-5</i> ; <i>Tween 81</i> .
Polysorbate 85	<i>Crillet 45</i> ; <i>Hodag PSTO-20</i> ; <i>Liposorb TO-20</i> ; <i>Montanox 85</i> ; sorbitan tri-9-octadecenoate poly(oxy-1,2-ethanediyl) derivatives; <i>Protasorb TO-20</i> ; <i>Tween 85</i> .
Polysorbate 120	<i>Crillet 6</i> .

3. Chemical Names and CAS Registry Numbers

See Table I.

Table I: Chemical name and CAS registry number of selected polysorbates.

Polysorbate	Chemical name	CAS number
Polysorbate 20	Polyoxyethylene 20 sorbitan monolaurate	[9005-64-5]
Polysorbate 21	Polyoxyethylene (4) sorbitan monolaurate	[9005-64-5]
Polysorbate 40	Polyoxyethylene 20 sorbitan monopalmitate	[9005-66-7]
Polysorbate 60	Polyoxyethylene 20 sorbitan monostearate	[9005-67-8]
Polysorbate 61	Polyoxyethylene (4) sorbitan monostearate	[9005-67-8]
Polysorbate 65	Polyoxyethylene 20 sorbitan tristearate	[9005-71-4]
Polysorbate 80	Polyoxyethylene 20 sorbitan monooleate	[9005-65-6]
Polysorbate 81	Polyoxyethylene (5) sorbitan monooleate	[9005-65-6]
Polysorbate 85	Polyoxyethylene 20 sorbitan trioleate	[9005-70-3]
Polysorbate 120	Polyoxyethylene 20 sorbitan monoisostearate	[66794-58-9]

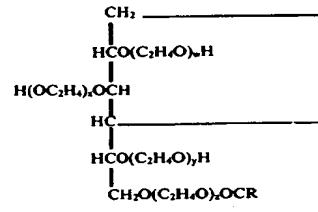
4. Empirical Formula Molecular Weight

Approximate molecular weights for selected polysorbates are shown below in Table II.

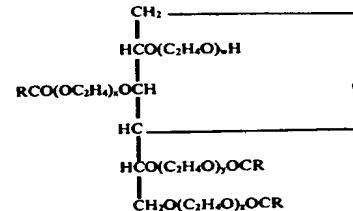
Table II: Empirical formula and molecular weight of selected polysorbates.

Polysorbate	Formula	Molecular weight
Polysorbate 20	$C_{58}H_{114}O_{26}$	1128
Polysorbate 21	$C_{26}H_{50}O_{10}$	523
Polysorbate 40	$C_{62}H_{122}O_{26}$	1284
Polysorbate 60	$C_{64}H_{126}O_{26}$	1312
Polysorbate 61	$C_{32}H_{62}O_{10}$	607
Polysorbate 65	$C_{100}H_{194}O_{28}$	1845
Polysorbate 80	$C_{64}H_{124}O_{26}$	1310
Polysorbate 81	$C_{34}H_{64}O_{11}$	649
Polysorbate 85	$C_{100}H_{188}O_{28}$	1839
Polysorbate 120	$C_{64}H_{126}O_{26}$	1312

5. Structural Formula



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

$w+x+y+z = 20$ (Polysorbate 20, 40, 60, 65, 80 and 85)
 $w+x+y+z = 5$ (Polysorbate 81)
 $w+x+y+z = 4$ (Polysorbate 21 and 61)

6. Functional Category

Emulsifying agent; nonionic surfactant; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides.

Polysorbates are hydrophilic nonionic surfactants used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions. They may also be used as solubilizing agents for a variety of substances including essential oils and oil soluble vitamins, and as wetting agents in the formulation of oral and parenteral suspensions. Polysorbates are also widely used in cosmetics and food products.

Use	Concentration (%)
Emulsifying agent	
Used alone in oil-in-water emulsions	1-15
Used in combination with hydrophilic emulsifiers in oil-in-water emulsions	1-10
Used to increase the water holding properties of ointments	1-10
Solubilizing agent	
For poorly soluble active constituents in lipophilic bases	1-10
Wetting agent	
For insoluble active constituents in lipophilic bases	0.1-3

8. Description

Polysorbates have a characteristic odor and a warm, somewhat bitter taste. Their colors and physical forms at 25°C are shown below in Table III.

Table III: Color and physical form of selected polysorbates at 25°C

Polysorbate	Color and form at 25°C
Polysorbate 20	Yellow oily liquid
Polysorbate 21	Yellow oily liquid
Polysorbate 40	Yellow oily liquid
Polysorbate 60	Yellow oily liquid
Polysorbate 61	Tan solid
Polysorbate 65	Tan solid
Polysorbate 80	Yellow oily liquid
Polysorbate 81	Amber liquid
Polysorbate 85	Amber liquid
Polysorbate 120	Yellow liquid

9. Pharmacopeial Specifications

Test	PhEur 1985	USPNF XVII
Identification		
Polysorbate 20	+	+
Polysorbate 40*	—	+
Polysorbate 60	+	+
Polysorbate 80	+	+
Saponification value		
Polysorbate 20	40-50	40-50
Polysorbate 40*	—	41-52
Polysorbate 60	45-55	45-55
Polysorbate 80	45-55	45-55
Hydroxyl value		
Polysorbate 20	96-108	96-108
Polysorbate 40*	—	89-105
Polysorbate 60	81-96	81-96
Polysorbate 80	65-80	65-80
Water		
Polysorbate 20	≤ 3.0%	≤ 3.0%
Polysorbate 40*	—	≤ 3.0%
Polysorbate 60	≤ 3.0%	≤ 3.0%
Polysorbate 80	≤ 3.0%	≤ 3.0%
Residue on ignition		
Polysorbate 20	—	≤ 0.25%
Polysorbate 40*	—	≤ 0.25%
Polysorbate 60	—	≤ 0.25%
Polysorbate 80	—	≤ 0.25%
Sulfated ash		
Polysorbate 20	≤ 0.2%	—
Polysorbate 60	≤ 0.2%	—
Polysorbate 80	≤ 0.2%	—
Arsenic		
Polysorbate 20	—	≤ 1 ppm
Polysorbate 40*	—	≤ 1 ppm
Polysorbate 60	—	≤ 1 ppm
Polysorbate 80	—	≤ 1 ppm
Heavy metals		
Polysorbate 20	≤ 10 ppm	≤ 0.001%
Polysorbate 40*	—	≤ 0.001%
Polysorbate 60	≤ 10 ppm	≤ 0.001%
Polysorbate 80	≤ 10 ppm	≤ 0.001%
Acid value		
Polysorbate 20	≤ 2.0	≤ 2.2
Polysorbate 40*	—	≤ 2.2
Polysorbate 60	≤ 2.0	≤ 2.2
Polysorbate 80	≤ 2.0	≤ 2.2
Iodine value		
Polysorbate 20	≤ 5.0	—
Polysorbate 60	≤ 5.0	—
Polysorbate 80	18-24	—
Reducing substances		
Polysorbate 20	+	—
Polysorbate 60	+	—
Polysorbate 80	+	—
Specific gravity		
Polysorbate 20	1.10	—
Polysorbate 60	1.10	—
Polysorbate 80	1.08	1.06-1.09
Viscosity at 25°C		
Polysorbate 80	400 mPa s	300-500 mm ² /s

* Note that the BP 1993 and PhEur 1985 contain monographs for polysorbate 20, 60 and 80; the USPNF XVII contains monographs for polysorbate 20, 40, 60 and 80.

10. Typical Properties

Acid value: see Table IV.

Acidity/alkalinity: pH 6.0-8.0 for a 5% w/v aqueous solution.

Flash point: 149°C

HLB value: see Table V.

Hydroxyl value: see Table IV.

Moisture content: see Table IV.

Saponification value: see Table IV.

Solubility: see Table VI.

Specific gravity: see Table V.

Surface tension: for 0.1% w/v solutions, see table below.

Polysorbate	Surface tension at 20°C (mN/m)
Polysorbate 21	34.7
Polysorbate 40	41.5
Polysorbate 60	42.5
Polysorbate 61	41.5
Polysorbate 80	42.5
Polysorbate 85	41.0

Viscosity (dynamic): see Table V.

Table IV: Typical properties of selected polysorbates.

Polysorbate	Acid value	Hydroxyl value	Moisture content (%)	Saponification value
Polysorbate 20	2.0	96-108	3.0	40-50
Polysorbate 21	3.0	225-255	3.0	100-115
Polysorbate 40	2.0	90-105	3.0	41-52
Polysorbate 60	2.0	81-96	3.0	45-55
Polysorbate 61	2.0	170-200	3.0	95-115
Polysorbate 65	2.0	44-60	3.0	88-98
Polysorbate 80	2.0	65-80	3.0	45-55
Polysorbate 81	2.0	134-150	3.0	96-104
Polysorbate 85	2.0	39-52	3.0	80-95
Polysorbate 120	2.0	65-85	5.0	40-50

Table V: Typical properties of selected polysorbates (continued).

Polysorbate	HLB value	Specific gravity at 25°C	Viscosity (mPa s)
Polysorbate 20	16.7	1.1	400
Polysorbate 21	13.3	1.1	500
Polysorbate 40	15.6	1.08	500
Polysorbate 60	14.9	1.1	600
Polysorbate 61	9.6	1.06	solid
Polysorbate 65	10.5	1.05	solid
Polysorbate 80	15.0	1.08	425
Polysorbate 81	10.0	—	450
Polysorbate 85	11.0	1.00	300
Polysorbate 120	14.9	—	—

Table VI: Solubilities of selected polysorbates in various solvents.

Polysorbate	Ethanol	Solvent		
		Mineral oil	Vegetable oil	Water
Polysorbate 20	S	I	I	S
Polysorbate 21	S	I	I	D
Polysorbate 40	S	I	I	S
Polysorbate 60	S	I	I	S
Polysorbate 61	SW	SW	SWT	D
Polysorbate 65	SW	SW	DW	D
Polysorbate 80	S	I	I	S
Polysorbate 81	S	S	ST	D
Polysorbate 85	S	I	ST	D
Polysorbate 120	S	I	I	S

D = dispersible; I = insoluble; S = soluble;
T = turbid; W = on warming.

11. Stability and Storage Conditions

Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation.

Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Discoloration and/or precipitation occurs with various substances, especially phenols, tannins, tars and/or tar-like materials. The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.⁽¹⁾ See Methylparaben.

13. Method of Manufacture

Polysorbates are prepared from sorbitol in a three step process. Water is initially removed from the sorbitol to form a sorbitan (a cyclic sorbitol anhydride). The sorbitan is then partially esterified with a fatty acid, such as oleic or stearic acid, to yield a hexitan ester. Finally, ethylene oxide is then chemically added in the presence of a catalyst to yield the polysorbate.

14. Safety

Polysorbates are widely used in cosmetics, food products and oral, parenteral and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials. There have however been occasional reports of hypersensitivity to polysorbates following their topical use. Polysorbates have also been associated with serious adverse effects, including some deaths, in low-birthweight infants administered intravenously a vitamin E preparation containing a mixture of polysorbate 20 and 80.^(2,3) The WHO has set an estimated acceptable daily intake for polysorbates 20, 40, 60, 65 and 80, calculated as total polysorbate esters, at up to 25 mg/kg body-weight.⁽⁴⁾

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Polysorbates 60, 65 and 80 are GRAS listed. Polysorbates 20, 40, 60, 65 and 80 are accepted as food additives in Europe. Polysorbates 20, 40, 60 and 80 are included in the FDA Inactive Ingredients Guide (IM, IV, oral, rectal, topical and vaginal preparations). Polysorbates are included in parenteral and nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Polysorbate	Pharmacopeia
Polysorbate 20	Aust, Br, Eur, Fr, Ger, Gr, Hung, Ind, It, Neth, Port, Swiss and USPNF.
Polysorbate 40	USPNF.
Polysorbate 60	Aust, Br, Cz, Eur, Fr, Ger, Gr, Hung, It, Neth, Port, Swiss and USPNF.
Polysorbate 80	Aust, Br, Braz, Chin, Cz, Eur, Fr, Ger, Gr, Hung, Ind, It, Jpn, Neth, Nord, Port, Rom, Swiss and USPNF.

18. Related Substances

Sorbitan Esters (Sorbitan Fatty Acid Esters)

19. Comments

20. Specific References

1. Blanchard J. Effect of polyols on interaction of paraben preservatives with polysorbate 80. *J Pharm Sci* 1980; 69: 169-173.
2. Alade SL, Brown RE, Paquet A. Polysorbate 80 and E-Ferol toxicity. *Pediatrics* 1986; 77: 593-597.
3. Balistreri WF, Farrell MK, Bove KE. Lessons from the E-Ferol tragedy. *Pediatrics* 1986; 78: 503-506.
4. FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications: seventeenth report of the joint FAO/WHO expert committee on food additives. *Tech Rep Ser Wld Hlth Org* 1974; No. 539.

21. General References

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Chowhan ZT, Pritchard R. Effect of surfactants on percutaneous absorption of naproxen I: comparisons of rabbit, rat, and human excised skin. *J Pharm Sci* 1978; 67: 1272-1274.

Donbrow M, et al. Autoxidation of polysorbates. *J Pharm Sci* 1978; 67: 1676-1681.

Smolinske SC. *Handbook of food, drug, and cosmetic excipients*. Boca Raton, FL: CRC Press Inc, 1992: 295-301.

22. Authors

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